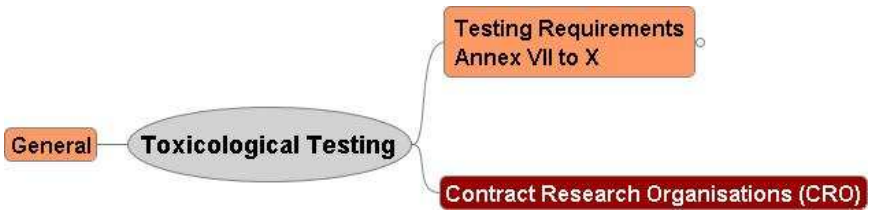
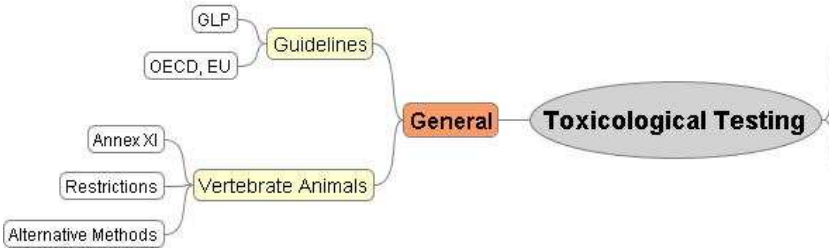
Toxicological Testing required by REACH

Norbert Bornatowicz / Toxicology

Overview on the presentation



Toxicological Testing - General



Guidelines (1)

- Good Laboratory Practice (GLP)
  mandatory for toxicological and ecotoxicological testing,

  not mandatory for physico-chemical testing
  => not compliant with other regulations or with non-EU member states

- EU methods: 67/548/EWG, Annex V (Part B)
  http://ecb.jrc.it/testing-methods/annex5/

- OECD method (Section 4: Health effects)
  http://titania.sourceoecd.org/vl=14974079/cl=11/nw=1/rpsv/periodical/p15_about.htm?jnlissn=1607310x

Guidelines (2)

- REACH, Art. 13 (3):
  "Where tests on substances are required to generate information on intrinsic properties of substances, they shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate."

- This Commission Regulation is still missing.
  A draft is available.
  The draft does not consider GHS and new alternative methods are not included.

Vertebrate Animals (1)

- "In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort."
  (Art. 25 (1))
- "New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted."
  (Annex VI, Step 4)
- "In accordance with Directive 86/609/EEC, it is necessary to replace, reduce or refine testing on vertebrate animals."
  (Preamble (47))

➡ We will consult **Annex XI**
(GENERAL RULES FOR ADAPTATION OF THE STANDARD TESTING REGIME SET OUT IN ANNEXES VII TO X)

Vertebrate Animals (2) / Annex XI

- **Testing does not appear scientifically necessary**
  - Use of existing data (not under GLP, not according to test methods, but adequate and reliable, historical human data)
  - Weight of evidence (sufficient weight of evidence from several independent sources of information or from the use of newly developed test methods or from an international test method recognised by the Commission or the Agency as being equivalent)
  - 'suitable' in vitro methods (sufficiently well developed [ECVAM criteria] for the entry into the prevalidation process):
    in general, negative results have to be confirmed by in vivo tests, unless scientifically validated or results are adequate for classification and labeling/risk assessment and adequate and reliable documentation of the method is available
  - (Q)SAR
  - Grouping of substances and read-across approach

Vertebrate Animals (3) / Annex XI

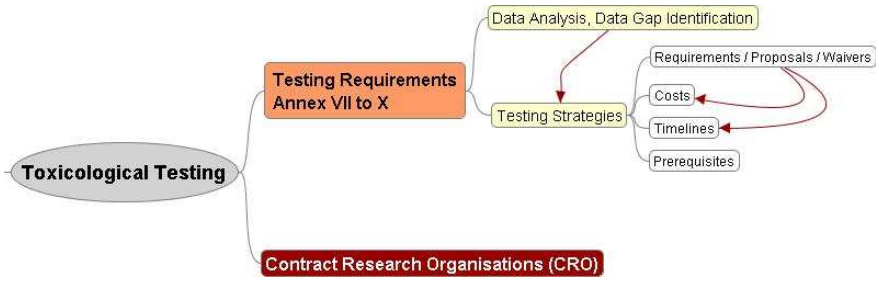
- **Testing is technically not possible**
  e.g. very volatile, highly reactive or unstable substances cannot be used, mixing of the substance with water may cause danger of fire or explosion or the radio-labelling of the substance required in certain studies may not be possible

- **Substance-tailored exposure-driven testing**
  Testing in accordance with Sections 8.6 and 8.7 of Annex VIII, Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report.
  (Annex VII, sections 8.6 and 8.7.: Repeated dose toxicity testing and Reproductive toxicity screening)

Vertebrate Animals (4) / Alternatives

- Only few alternative methods validated and available as guidelines
- More alternative methods may be available in the future
- Available alternative methods only for 'cheap' in vivo studies
  and in the majority of cases additive to the 'cheap' studies, making them 'expensive'

Toxicological Testing – Testing Requirements



Data Analysis, Data Gap Identification

- Collection and compilation of existing data — chemist, HSE officer, product safety
  - Own data (clarification of data ownership)
  - Data from literature
    some sources:
    - http://ecb.jrc.it/qsar/information-sources/
    - http://www.epa.gov/chemrtk/pubs/general/sources1.htm
  - Data from SIEF participants
  - Data from chemically related substances (grouping, read-across)
- Data evaluation — toxicologist
  - Are the data reliable, relevant, adequate?
  - Identification of key studies for the relevant endpoints or 'worst case scenario'
- Data Gap Identification — toxicologist

Testing Strategies – Requirements / Proposals

- Data requirements are <u>additive</u>, depending on the production/imported volume per year
  - ≥1 t/a: Annexes VI + VII
  - ≥10 t/a: Annexes VI + VII + VIII
  - ≥100 t/a: Annexes VI + VII + VIII + IX
  - ≥1000 t/a: Annexes VI + VII + VIII + IX + X
- Toxicological tests with vertebrate animals:
  request to ECHA and/or SIEF participants for existing data is mandatory
- Toxicological tests with vertebrate animals, listed in Annexes VII and VIII:
  mandatory (but there are exemptions)
- Toxicological tests with vertebrate animals, listed in Annexes IX and X:
  only to be proposed in the technical dossier/chemical safety report

Testing Strategies – Waivers (1)

- Annexes VII to X:
  - Column 1: Standard information required
  - Column 2: Specific rules for adaptation from column 1:
    "… specific rules according to which the required standard information may be omitted, replaced by other information, provided at a different stage or adapted in another way."

COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	
8.3.	Skin sensitisation The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human, animal and alternative data, (2) *In vivo* testing.	8.3.	Step 2 does not need to be conducted if: — the available information indicates that the substance should be classified for skin sensitisation or corrosivity, or — the substance is a strong acid (pH ≤ 2,0) or base (pH ≥ 11,5), or — the substance is flammable in air at room temperature. The Murine Local Lymph Node Assay (LLNA) is the first-choice method for *in vivo* testing. Only in exceptional circumstances should another test be used. Justification for the use of another test shall be provided.

Testing Strategies – Waivers (2)

- Consider also Annex XI

➡ Scientific and substance-tailored approaches to testing (testing strategies) are supported

➡ Testing strategies are not always easy to understand

➡ Sound cost estimates are not possible.

Toxicological Studies Required by Annex VII

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 1 t/a, Annex VII										
Skin irritation or corrosion in vitro										
Eye irritation in vitro										
Skin sensitization										
Mutagenicity: in vitro gene mutation study in bacteria										
Acute toxicity by oral route										

- Step 1: an assessment of the available human and animal data
- Step 2: an assessment of the acid or alkaline reserve
- Step 3: *in vitro* study for skin corrosion
- Step 4: *in vitro* study for skin irritation

Toxicological Studies Required by Annex VIII

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 10 t/a, Annex VIII										
Skin irritation in vivo										
Eye irritation in vivo										
Mutagenicity: in vitro cytogenetic study in mammalian cells or in vitro micronucleus test										
Mutagenicity: in vitro gene mutation study in mammalian cells										
Acute toxicity by inhalation or by dermal route										
Repeated dose toxicity: 28 days (**most appropriate route of administration**)										
Reproduction toxicity: Screening test										

Toxicological Studies to be proposed according to Annex IX

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 100 t/a, Annex IX										
Mutagenicity: in vivo somatic cell genotoxicity study										
Repeated dose toxicity: 90 days (most appropriate route of administration)										
Reproductive toxicity: Pre-natal developmental toxicity										
Reproductive toxicity: Two-generation reproduction toxicity										

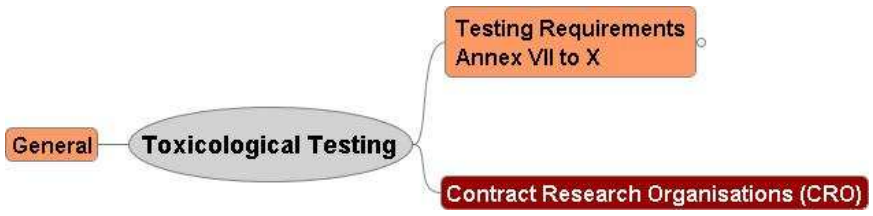
Toxicological Studies to be proposed according to Annex X

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 1000 t/a, Annex X										
Mutagenicity: second in vivo somatic cell genotoxicity study										
Repeated dose toxicity: ≥ 12 months										
Specific toxicological studies (neurotoxicity, immunotoxicity etc.)										
Further reproduction toxicity studies										
Carcinogenicity study										

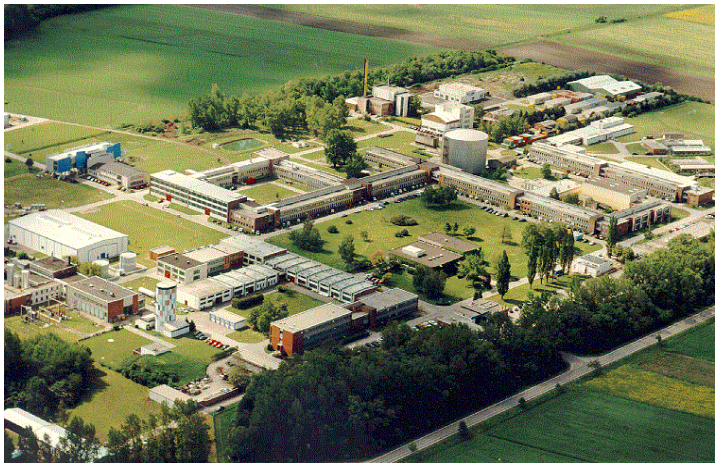
Testing Costs (Toxicological Studies)

- No sound estimates can be given
- However, if you want some figures:
  - ≥1 t/a: 13 000 Euro
  - ≥10 t/a: + >120 000 Euro
  - ≥100 t/a: + >400 000 Euro
  - ≥1000 t/a: + >900 000 Euro
- Low testing capacities may result in higher prices

ARC Toxicology



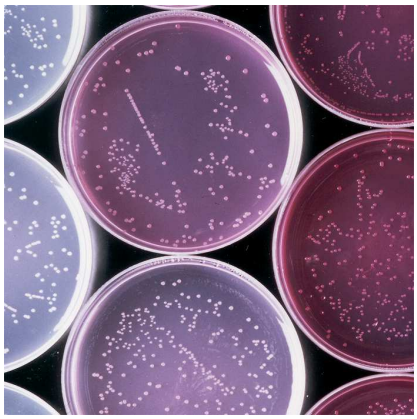
ARC Toxicology, Location Seibersdorf



ARC Toxicology

- CRO for Toxicology, Ecotoxicology and physico-chemical properties
- GLP
- In the market for more than 25 years
- > 36 staff, long-term experience,
  4 'Masters of Toxicology',
  3 EUROTOX registered toxicologists
- In vitro and in vivo studies,
  inhalation toxicity
- Animal houses, histopathology,
  pathologist

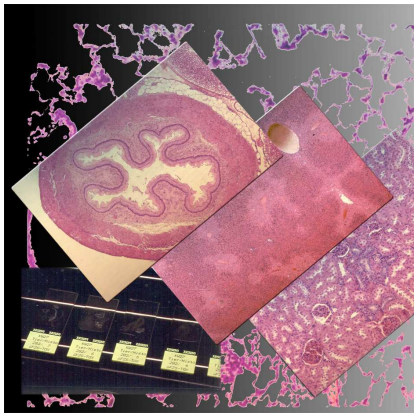
ARC Toxicology – Our Services



- Studies
- Consulting
- Research

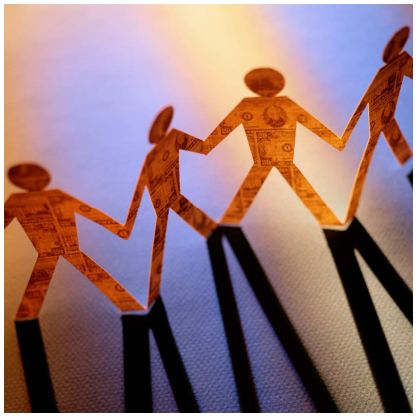
→ Package

ARC Toxicology – Testing Services



- Short and long term toxicity
- Mutagenicity, carcinogenicity
- Immunotoxicity
- Reproduction
- Toxicokinetics, skin penetration
- Ecotoxicity
- Physico-chemical properties

ARC Toxicology – REACH Consulting



- Data evaluation, identification of data gaps, literature search
- Compilation and writing of notification and registration dossiers
- Write-up of robust summaries
- Write-up of Chemical Safety Reports (CSA's)
- Write-up of IUCLID files
- Development of testing strategies, support for waiving, presentation to authorities

ARC Toxicology: Vienna is very near – and so are we

Austrian Research Centers GmbH – ARC
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This presentation will be available on
www.lifesciences.at/toxicology

Terms defined by Klimisch et al.

Zur Bewertung von vorhandenen Berichten:

- **Reliability** - evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings;
- **Relevance** - covering the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation; and
- **Adequacy** - defining the usefulness of data for hazard/risk assessment purposes.